REMARKS

Applicants acknowledge, with appreciation, entry of the amendments filed June 7, 2005. Claims 8, 14, 16-22 and 25 are currently under examination.

Applicants have amended claims 8, and 16-22 to include the word "isolated" as helpfully suggested by the Examiner.

Applicants have amended claim 16 to replace the term "that flank" with "flanking" as helpfully suggested by the Examiner in order to clarify the claim language.

Applicants have amended claims 8 and 14 to replace the terms "the method of claim 16" and "the method of claim 25" with "according to claim 16" and "according to claim 25," respectively. It is believed that the claims are in proper form for allowance.

Applicants have amended claims 16, 22 and 25 to include the feature that the cells are entrapped in a matrix that is disposed to receive cells for transplantation. Support for the amendment may be found in the specification , for example, at page 6, lines 3-12. No new matter is added.

35 U.S.C. § 112, first paragraph (Enablement)

Applicants submit that the cell line NKNT-3 will be deposited according to the terms of the Budapest Treaty and an appropriate affidavit will be submitted to the Patent Office. Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, for claim 22 be held in abeyance until such deposit can be made.

The Office Action also rejects claims 8, 14, 16-21 and 25 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled because the DNA constructs could include non-integrating vectors which would be eliminated from the cells and hence the cells would not be immortalized.

Applicants note that the DNA constructs of the claims contain two recombinase target cites flanking the oncogene. Thus, such DNA constructs become integrated into the genome of the cell and immortalize the cell. Applicants invite the Examiner's attention to Soukharev *et al.* (1999) "Segmental genomic replacement in embryonic stem cells by double *lox* targeting" *Nucl. Acids Res.* 27(18):e21 ("Soukharev") where it is shown that Bluescript vectors (non-retroviral) containing recombination sites could be introduced into cells by

electroporation to insert the target gene into cells by homologous recombination. This shows that the DNA constructs of the invention do not have to be retroviral and that the constructs described in the specification, which do not have to be retroviral vectors, can be successfully used according to the methods of the invention without undue experimentation.

Applicants earnestly submit that the claims are enabled by the specification as evidenced by Soukharev. Withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

35 U.S.C. § 102/103

The Office Action rejects claims 14 and 25 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 6,130,364 to Jakobovits *et al.* ("Jakobovits"). Applicants respectfully disagree.

Jakobovits teaches that transgenic animals expressing a full complement of human immunoglobulin genes may be used in the method of the invention (See col. 7, lines 46-55). Transgenic mice containing a full complement of human immunoglobulin genes is taught, for example, by Kucherlapati *et al.,* in PCT Publication No,. WO 91/10741 and in PCT Publication No. WO 94/02602 (see Col. 13, lines 16-19). In the method of the invention a single *lox* site may be inserted into the mouse genome adjacent to or into the immunoglobulin locus in "whatever vector is used to insert the immunoglobulin loci." (Col. 13, lines 30-40 (citing Kucherlapati)). Presumably, all of the cells of the transgenic animal would be so modified.

However, Jakobovits teaches that only the lymphocytic cells ("hybridomas") would be used to transfect the targeting vector with a transient expression of *cre* such that homologous recombination would occur (see for example, col. 15, lines 43-52; col. 20, lines 20-34; col. 22, lines 20-30). Thus, the second *lox* sequence would be inserted into lymphocytes, *not* hepatocytes. Thus, Jacobovits does not teach a hepatocyte having *two lox* sites, as recited in the claims. Thus, Jacobovits does not anticipate claims 14 and 25.

Further, nothing in Jacobovits teaches or suggests that the transgenic mice should have two *lox* sites integrated into the mouse genome. It is the targeting vectors which contain the *lox* site which recombines in conjunction with *cre* expression. Thus, it would be against

the operating principle of Jakobovits to insert two *lox* sites in the transgenic animals genome. Thus, Jakobovits also does not render claims 14 and 25 obvious under 35 U.S.C. § 103.

Finally the cited art does not teach the feature of entrapping the cells in a matrix for transplantation.

Withdrawal of the rejection is respectfully requested.

35 U.S.C. § 103(a)

The Office Action rejects claims 8, 14, 16-20 and 25 under 35 U.S.C. § 103(a) as obvious over Nakamura *et al.* (1996) *Transplant* 63:1541-1547 ("Nakamura") in view of U.S. Patent No. 5,629,159 to Anderson ("Anderson") and Adams *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89(19):8981-8985 ("Adams").

Neither Nakamura nor Anderson, alone or in combination, teach reverse-immortalixed hepatocytes entrapped in a matrix for transplantation. Indeed, Nakamura teaches that intrasplenic and intraperitoneal engraftment of free primary or conditionally-immortalized hepatocytes was effective in improving survival. There was no attempt to restrict the migration of hepatocytes. In fact, the migration of hepatocytes from the spleen to the liver was beneficial.

The Office Action also rejects claim 21 under 35 U.S.C. § 103(a) as obvious over Nakamura and Anderson as applied to claims 8, 14, 16-20 and 25, and further in view of Adams. As stated above, the cited art (either alone or in combination) does not teach or suggest reversibly-immortalized hepatocytes in a matrix for transplantation. One of skill in the art would not have a reasonable expectation of success that reverse-immortalized hepatocytes entrapped in a matrix would be would be useful as transplanted hepatocytes to regain liver function. Withdrawal of the rejection is respectfully requested.

Applicants earnestly submit that the claims are in proper form for allowance and distinguish over the art of record. Upon making the deposit under the Budapest Treaty and filing the appropriate affidavit, Applicants submit that the claims will be in condition for allowance.

Respectfully submitted,

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